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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,532	01/25/2002	Jeffrey A. Lyon	003/240/SAP	2344

7590 07/07/2005

ATTN: MCMR-JA (Ms. Elizabeth Arwine-PATENT ATTY)
U. S. Army Medical Research and Materiel Command
504 Scott Street
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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,532	LYON ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5 and 7-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3* is/are allowed.

6)☒ Claim(s) *1, 5 and 7-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment

1. The response filed on 4/1/05 has been entered into the record.

Status of Claims

2. Claims 1, 3 and 5 have been amended.

Claims 2, 4 and 6 are cancelled.

New claims 12-16 have been added

Claims 1, 3, 5 and 7-16 are pending and are under examination in the application.

Claim Rejections - 35 U.S. C. § 112, second paragraph withdrawn

3. In view of amendment to the claims, the rejection under 35 U.5.C. 112, second paragraph is withdrawn.

Claim Rejections - 35 USC 112, first paragraph maintained

4. The rejection of claims 1, 5, and 7-16 under 35 USC 112 first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention is maintained as set forth in the previous office action.

Claim 1 is drawn to a vaccine comprising a C-terminal 42kD fragment of merozoite surface protein, MSP-1_{42}, SEQ.ID.NO: 2 from *Plasmodium falciparum* 3D7 and an adjuvant. Claims 5-16 are drawn to a method of inducing protective immune response to malaria comprising administering a composition comprising *P. falciparum* 3D7,MSP-1_{42} SEQ.ID.NO: 2 and an adjuvant.

The specification lacks enabling disclosure for a vaccine or for a method of inducing protective immune response comprising administering a composition comprising a C-terminal 42kD fragment of merozoite surface protein, MSP-1_{42}, SEQ.ID.NO: 2 from *Plasmodium falciparum* 3D7 and an adjuvant selected from the group consisting of A, B, C, D and E that would protect a mammal against malaria infection caused by the *Plasmodium falciparum* for the following reasons:

The specification discloses the isolation and purification of the protein from *P. falciparum* 3D7, SEQ.ID.NO: 2. The specification also teaches on page 59(example 2) the potency of the claimed composition (candidate vaccine) by immunizing mice with the claimed composition.

Mice were seroconverted indicating that it is an immunogenic composition. Further, safety and immunogenicity of the product was assessed by biochemical and hematological laboratory tests in rhesus monkeys immunized up to five times and no adverse local responses were observed and all tests were normal. On page 64, immunological studies in animals indicated that the composition used induced a specific antibody response as measured by ELISA (Table 4A) and IFA (Table 4B). The composition also induced cellular Immunity as measured by different cytokine response profiles (Table 5). However, the specification fails to disclose
(1) Animals immunized with claimed immunogenic composition are able to inhibit malaria infection upon challenge either with homologous or heterologous *Plasmodium falciparum.*
(2) The specification lacks correlation between *in vitro* results and *in vivo* results. The specification does not show that the anti- MSP-1_{42} antibodies were protective against malaria infection. Page 64, immunological studies in animals indicated that the composition used induced a specific antibody response as measured by ELISA (Table 4A) and IFA (Table 4B). However, the specification fails to provide positive correlation between the ELISA titer, the IFA titer and protection, which suggests that MSP-1_{42} might serve as good candidate vaccine.

The state of the art with respect to effective vaccine against *P.falciparum* is at developmental stage in identifying an effective antigen with respect to erythrocytic stage that could be used as a candidate vaccine. Egan et al (Infection and Immunity 1995, 63: 456-466) while testing MSP-1_{19} candidate vaccine antigen state (page 462, right column) " antibodies that recognize epitopes within the Pf MSP-1_{42} and PfMSP-1_{19} (processing products of PfMSP-1) may be involved in protective immunity in malaria" because human sera can inhibit the binding of monoclonal antibodies whose epitopes map to either EGF motif or Mabs, which recognize the double motif structure. However, none of the Mab could inhibit binding of human antibodies. Thus human sera recognize a number of epitopes within MSP-1_{19}". Therefore, induction of malaria-specific antibodies that recognize critical epitopes on MSP-1 is important. While testing synthetic malaria peptide vaccine with various adjuvants Kashala state (Vaccine, 2002,20; 2263-2277,page 2276, first column), "Knowledge of protective immunity in malaria is still incomplete. It is generally believed that induction of malaria-specific antibodies is critical, but perhaps not sufficient for an effective control of human malarial infections perhaps not sufficient for an effective control of human malarial infections". Further, when developing a multiantigen, multistage vaccine candidate, Tine et al 1996 (Infection and Immunity 1996, 64: 3833-3844) state " although in vitro assays of immune function do exist, none correlate with protection". Further, Angov et al (Molecular and Biochemical Parasitology 2003, 128; 195-204) showed that the antibody obtained from rabbits immunized with a composition comprising FMPI (vaccine candidate antigen 3D7, MSP-1_{42}) inhibited 3D7 parasite invasion less efficiently than the FVO strain (see Table 2) in *in vitro* inhibition assays. Further, inhibition of P.falciparum 3D7 invasion appears to depend on multiplication rate of invasion cycle of the parasite as rate of invasion appears to be faster in strain 3D7 than FVO. Therefore, it suggests that the recombinant protein has not, as yet, been shown to generate protective antibodies, which would be expected of a vaccine against *P.falciparum.* Thus, it is apparent identification of a protective erythrocytic candidate vaccine against P.falciparum is yet to be identified.

In addition, the specification (page 23) defines vaccine as an immunogenic composition capable of eliciting protection against malaria, whether partial or complete. A vaccine may also be useful for treatment of an infected individual, in which case ii is called a therapeutic vaccine. The term therapeutic refers to a composition that is capable of treating malaria infection. Similarly, the medical Dictionary defines Pharmaceutical composition as "relating to pharmacy or to pharmaceutics"; "pharmacy" as "the practice of preparing and dispensing drugs", and "drug" as "Therapeutic agent; any substance, other than food, used in the prevention,

alleviation, treatment, or cure of disease". While the definition of "pharmaceutical" is broad, it is not so broad to cover **any** use of a substance on or in the body of a subject, only those uses intended to prevent, alleviate, treat, or cure a disease within the animal to which the substance was administered.

In view of these definitions, in the instant application, the animal to which the claimed immunogenic composition is administered is merely being used as a bioreactor to make the antibodies. However, the instant specification does not teach how to use the claimed composition as a vaccine/pharmaceutical composition without undue experimentation, for the prevention, alleviation, treatment, or cure of a disease in the animal to which the substance is administered as defined by the specification.

Thus considering the state of the art in inhibiting malaria as indicated above, in view of definition of vaccine/pharmaceutical composition provided by the instant specification as well as by medical dictionary, the specification fails to provide sufficient evidence whether the claimed vaccine composition partially or completely inhibited the malaria infection upon challenge. Therefore, the skilled artisan would not be able to use such broadly claimed vaccine/ pharmaceutical composition or using said composition in a method for inducing protective immune response, in view of the unpredictability of the art in inhibiting different strains of *P.falciparum,* the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as broadly claimed.

Applicants' arguments filed on 4/1/05 and the Declaration provided by Dr. Jefferey Lyon have been fully considered but they are not deemed to be persuasive.

Applicant states that the claims 1, 5 and 7-1 1 were rejected under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure without evidence that the claimed vaccine and method produce a protective immune response and brings the Examiner's attention is directed to the Declaration of Dr. Jeffery Lyon, one of the inventors on the application, filed herewith, that presents challenge data in Aotus monkeys. Animals underwent a series of vaccine injections with a vaccine according to the invention, and were subsequently challenged by exposure to the FVO strain of P.falciparum. The vaccine of the invention produced a significant reduction in infection by P.falciparum, as shown in Figure 3 of the Declaration.

The Declaration provided by Dr. Jeffery Lyon filed on 4/1/05 (under 37 CFR 1.131? or 37 CFR 1.132?) has been considered but found to be insufficient to overcome the rejection of

record. The Declaration provided is not commensurate in scope with the specification and claims for the following reasons:

i The declaration states that the recombinant protein referred to as FMP1 is the MSP-1_{42} gene fragment. However, it is not clear what is the GMP protein. Further, it is not clear SEQ.ID.NO: 2 as claimed is the same as FMP-1 or GMP protein.

ii. The specification does not set forth that Aotus monkeys do not get infected with 3D7 and get infected with FVO. However, the specification teaches about Rhesus monkey. Rhesus monkeys were immunized with the claimed composition induced an antibody response. The declaration indicates that Aotus monkey were vaccinated with 3D7 and challenged with FVO. It appears that Kumar et al 1995 (Molecular Medicine) used in the previous prior art rejections disclosed the composition FVO MSP-1_{42} to immunize Aotus monkeys and challenged with FVO would read on the claimed invention.

iii. Adjuvant AS02A is not described in the specification or in the claims.

iv. The declaration indicates that the claimed composition inhibits the parasitaemia and thereby can be used in a method to inhibit or treat parasitaemia caused by Plasmodium falciparum. Therefore, the rejection is maintained.

Remarks

5. Claim 3 is allowed.

Claims 1, 5, 7-16 stand rejected.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

7. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number for submission of before-final amendments is (703) 872-9306. The Right Fax number for submission of after-final amendments is (703) 872-9307.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Padma Baskar

MARK NAVARRO
PRIMARY EXAMINER